Recapitulating pancreatic cancer ecosystems by multicellular cancer organoid cultures based on patient-derived cancer cells

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Cancer ecosystems comprise not only of cancer cells but also of various stromal cells, such as mesenchymal and vascular endothelial cells. Pancreatic cancer is stromal-rich cancer, and the abundant stroma is considered to responsible for the resistance to treatment and for poor prognosis. Contrary to expectations, however, treatment targeting stromal mesenchymal cells exacerbates pancreatic cancer. Accordingly, it is important to understand and control pancreatic cancer cell- stromal cell interaction rather than merely targeting the stroma. In order to analyze the cancer cell- stromal cell interaction and further accurately assess the susceptibility of pancreatic cancer drugs, a culture system capable of reproducing pancreatic cancer ecosystem is essential.

We previously established a method to generate multi-lineage functional organs using human iPS cells. Autonomous cell aggregation is induced by co-culturing human iPS cell-derived hepatic endoderm, vascular endothelial cells, mesenchymal cells under certain conditions results in the generation of the liver primordia i.e. iPSC liver bud (Takebe T, Sekine K et al, Nature, 2013; Takebe T, Sekine K et al., Cell Reports, 2017). Furthermore, single-cell RNA sequencing analysis elucidated the dynamic cell-cell interaction of different cell types (Sekine K, Camp JG et al, Nature 2017).

By applying the three-dimensional tissue reconstruction technique to pancreatic cancer research, we succeeded in reconstituting human pancreatic cancer tissue (pancreatic cancer organoid) recapitulating abundant stroma from patient-derived primary cancer cells. Evaluation of drug susceptibility of pancreatic cancer organoids in vitro revealed that drug sensitivity to gemcitabine, a therapeutic drug for pancreatic cancer, is greatly reduced compared to the cancer cell. Transplantation of cancer organoid into immunodeficient mice generated pancreatic cancer xenografts with abundant stroma and pancreatic ductal structures, which resembled patient pancreatic cancer tissue. Furthermore, drug sensitivity of the xenograft was also significantly decreased. We found cancer cell- stromal cell interaction is responsible for the treatment resistance of pancreatic cancer organoids xenograft.

In summary, pancreatic cancer organoids are an effective tool for reproducing the treatment resistance of pancreatic cancer patients and useful for drug screening.

[References]

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